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Bypass of a hydrocarbon adduct in an oligonucleotide template mediated by mispairing adjacent to the adduct.

Hruszkewycz AM, Dipple A.

Chemistry of Carcinogenesis Laboratory, ABL-Basic Research Program, NCI-Frederick Cancer Research and Development Center, MD 21702-1201.

The action of DNA polymerase (Sequenase Version 2.0) on an oligonucleotide template containing a 7-bromomethyl-benz[a]anthracene-deoxyadenosine adduct flanked by thymidine residues was investigated. The polymerase incorporated deoxyadenosine or deoxyguanosine residues opposite the thymidine 3' to the adduct with similar efficiencies. Whereas the normal A.T base pair led to arrest of polymerase progression along the template, formation of the G.T mismatch allowed incorporation of thymidine opposite the adduct and further primer extension. This mispair-mediated bypass was also seen with AMV reverse transcriptase and may represent a novel mechanism for overcoming the replication block of a bulky carcinogen--DNA adduct.

PMID: 1718621 [PubMed - indexed for MEDLINE]

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Factors that influence the mutagenic patterns of DNA adducts from chemical carcinogens.

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Carcinogens are generally mutagens, which is understandable given that tumor cells grow uncontrollably because they have mutations in critical genes involved in growth control. Carcinogens often induce a complex pattern of mutations (e.g., GC-->TA, GC-->AT, etc.). These mutations are thought to be initiated when a DNA polymerase encounters a carcinogen-DNA adduct during replication. In principle, mutational complexity could be due to either a collection of different adducts each inducing a single kind of mutation (Hypothesis 1a), or a single adduct inducing different kinds of mutations (Hypothesis 1b). Examples of each are discussed. Regarding Hypothesis 1b, structural factors (e.g., DNA sequence context) and biological factors (e.g., differing DNA polymerases) that can affect the pattern of adduct mutagenesis are discussed. This raises the question: how do structural and biological factors influence the pattern of adduct mutagenesis. For structural factors, three possibilities are considered: (Hypothesis 2a) a single conformation of an adduct giving rise to multiple mutations -- dNTP insertion by DNA polymerase being influenced by (e.g.) the surrounding DNA sequence context; (Hypothesis 2b) a variation on this ("dislocation mutagenesis"); or (Hypothesis 2c) a single adduct adopting multiple conformations, each capable of giving a different pattern of mutations. Hypotheses 2a, 2b and 2c can each in principle rationalize many mutational results, including how the pattern of adduct mutagenesis might be influenced by factors, such as DNA sequence context. Five lines of evidence are discussed suggesting that Hypothesis 2c can be correct for base substitution mutagenesis. For example, previous work from our laboratory was interpreted to indicate that [+ta]-B[a]P-N(2)-dG in a 5'-CGG sequence context (G115) could be trapped in a conformation giving predominantly G-->T mutations, but heating caused the adduct to equilibrate to its thermodynamic mixture of conformations, leading to a decrease in the fraction of G-->T mutations. New work is described suggesting that

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[+ta]-B[a]P-N(2)-dG at G115 can also be trapped predominantly in the G-->A mutational conformation, from which equilibration can also occur, leading to an increase in the fraction of G-->T mutations. Evidence is also presented that the fraction of G-->T mutations is higher when [+ta]-B[a]P-N(2)-dG at G115 is in ss-DNA (approximately 89%) vs. ds-DNA (approximately 66%), a finding that can be rationalized if the mixture of adduct conformations is different in ss- and ds-DNA. In summary, the factors affecting adduct mutagenesis are reviewed and five lines of evidence that support one hypothesis (2c: adduct conformational complexity can cause adduct mutational complexity) are discussed.

Publication Types:

- Review
- Review, academic

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